REMARKS

On page 2 of the Office Action, the Examiner maintains the rejection of Claims 9-10 under 35 U.S.C. § 103 as being unpatentable over Slavin et al in view of Ildstad et al and Zhang et al for the reasons of record.

The Examiner maintains his position that Slavin et al teaches a method for inducing immunological tolerance in organ transplantation recipients by subjecting the recipient to sub-lethal total body irradiation (TBI), and administering to the recipient whole bone marrow cells (WBMC). The Examiner notes that Slavin et al does not teach sub-lethal TBI of at least 6.5 Gy or 6.5 Gy to 7.0 Gy and administering whole blood marrow cells by hepatic portal administration. However, the Examiner contends that Ildstad et al teaches advantages of using TBI and that bone marrow engraftment is achieved in 100% of the recipients at 7.0 Gy. Further, the Examiner states that Zhang et al teaches portal vein administration of bone marrow cells. Hence, the Examiner maintains that it would have been obvious to combine the teachings of the cited references to achieve the present invention.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

Slavin et al teaches a technique of inducing immunological tolerance in a recipient by subjecting the recipient to sublethal total body irradiation (TBI) and administering to the recipient whole bone marrow cells (WBMC).

However, Slavin et al does <u>not</u> teach achieving an engraftment rate of 100% by employing a technique wherein an

organ is transplanted into a recipient within the same day (one-day protocol) as the WBMC administration, as claimed in the present invention.

More specifically, the technique taught by Slavin et al is fundamentally different from that of the present invention in terms of the following:

(i) TBI is conducted at an irradiation dose of 4.0 Gy (see Examples 10 and 11) in Slavin et al, not at least 6.5 Gy, as claimed in the present invention;

(ii) The WBMC administration route in Slavin et al is intravenous (i.v.) (see Column 29, line 2 and Column 36, line 15), not portal venous (p.v.) administration, as claimed in the present invention;

(iii) Slavin et al does not disclose transplanting an organ into a recipient who has undergone TBI within the same day as the WBMC administration, as claimed in the present invention; and

(iv) Slavin et al does not disclose that an engraftment rate of 100% is achieved by employing the transplantation technique as described in item (iii) above, as claimed in the present invention.

On page 3 of the Office Action, the Examiner contends that Slavin et al teaches that "if TBI is used it should be at a dose level that causes no severe or irreversible pancrytopenia" (see column 8, lines 57-67 thereof).

Column 8, lines 57-67 of Slavin et al teaches an: "ionizing radiation such as TLI and TBI. Due to its non-selective effects on all of the host's hematopoietic cells and its severe immediate and long-term side effects, TBI is not preferred (Emphasis added)."

Based on the above it is clear that the portion of Slavin et al cited by the Examiner can not be interpreted to mean that TBI can be employed in an equivalent manner as TLI in the teachings of Slavin et al. Rather, such should be interpreted to mean that TBI can somehow induce immunological tolerance: however, unlike TLI, TBI is by no means a preferable method.

Furthermore, as is clear from the above citation in Slavin et al, the irradiation dose taught by Slavin et al should be as low as possible so as not to cause severe side-effects. The irradiation dose specifically disclosed in Examples 10 and 11 of Slavin et al is "400 cGY", i.e., 4.0 Gy, which is much less than that of the present invention (at least 6.5 Gy). Thus, it is clear that Slavin et al does not teach or suggest "subjecting the recipient to TBI, using a sublethal irradiation dose of at least 6.5 Gy", as claimed in the present application.

The Examiner also contends that Slavin et al teaches that transplanting an organ into a recipient occurs within the same day as whole bone cells are administered (see column 13, lines 50-67; column 14, lines 10-15 and Example 14 thereof).

However, the cited portions of Slavin et al relied upon by the Examiner relate to Example 14 thereof, and the method disclosed in Example 14. Example 14 does not employ TBI, but

employs TLI. Slavin et al teaches that a one-day protocol is possible when TLI is employed, but nowhere teaches or suggests that a one-day protocol is also applicable when TBI is employed, as claimed in the present invention.

It is noted that the Examiner contends that Slavin et al teaches, in Example 14, achieving an engraftment rate of 100%.

However, Slavin et al discloses that a 100% engraftment rate was achieved when TLI was employed. Slavin et al does not teach or suggest to one or ordinary skill in the art that 100% engraftment could also be achieved when TBI is employed. In this regard, Slavin et al teaches the engraftment rate actually achieved by TBI is not higher than 80% (see Figs. 4 and 7 of Slavin et al).

As discussed above, prior to the present invention, it was presumed that, unlike the technique employing TLI, as employed in Slavin et al, the technique employing TBI as disclosed in Slavin et al, could not be used for organ transplantation (see Examples 10 and 11). Slavin et al does not teach or suggest that a one-day protocol is applicable by employing a technique using TBI, nor that 100% engraftment can be achieved by employing TBI, as claimed in the present application.

Applicants respectfully submit that the Examiner is improperly picking and choosing teachings in Slavin et al to combine, when in fact, Slavin et al does not provide any motivation for such combination.

Accordingly, Applicants respectfully submit that Slavin et al does not teach or suggest the present invention, and for the following reasons, it is clear that the combination

thereof with Ildstad et al and Zhang et al can only be made in hindsight, which is legally improper.

The Examiner refers to column 9, lines 15-20 of Ildstad et al, where it is explicitly stated that "the importance of the hematopoietic niches or "space" contributed by the low dose of TBI is even more evident when TBI is given one week prior to bone marrow transplantation [BMT]...".

A person skilled in the art would interpret the above description as evidence for the advantage of using TBI in a method involving the mixed allogeneic chimeras disclosed in Ildstad et al, i.e., a method for "repairing" host bone marrow cells.

On the other hand, in the present invention, tolerance is induced by "replacing" host bone marrow cells with donor bone marrow cells. Ildstad et al does not disclose the advantage attained by TBI in the method of the present invention.

Indeed, in the present invention, TBI was performed one day prior to BMT (see page 28, line 20, page 29, line 24 of the present specification and (6) of Test Example 4) instead of one week prior to BMT as taught by Ildstad et al. Claim 9 has been amended to clearly set forth such.

Moreover, Ildstad et al nowhere teaches or suggests administering donor's WBMCs one day after TBI by p.v. and performing organ transplantation on the same day of p.v. administration, as claimed in the present application.

The organ transplantation taught by Ildstad et al is conducted 1 to 7 months after BMC administration (see column 21, line 65). Such a technique is not applicable to organ

transplantation, wherein, e.g., the organs are derived from brain dead donors, as is preferable in organ transplantation. This is because the brain function of the donor has totally ceased after 24 hours.

In contrast, the technique of the present invention employing TBI is advantageous in that a 100% engraftment rate can be achieved by one-day protocol. Ildstad et al does not teach such an advantage.

The Examiner also contends that Ildstad et al teaches that bone marrow engraftment after sublethal total body irradiation is reliably achieved in 100% of recipients at 7.0 Gy (Figure 1 and column 17, specifically lines 4-25).

However, the above portion of Ildstad et al indicates that 100% of animals attained mixed chimerism. This is clear from the description "% recipients with chimerism" of the vertical axis of Fig. 1. This is entirely different from the effects of the present invention, i.e., "transplanting an organ into said recipient, to thereby achieve an engraftment rate of 100%".

Contrary to the Examiner's contention, Figure 7 of Ildstad et al does not show a 100% acceptance of skin grafts after 30 days; the only skin grafts showing no rejection after 30 days are (unsurprisingly) those of the recipients themselves (not the donor's skin). In contrast, donor-specific grafts were already approximately 10% rejected after 20 days.

As discussed above, Ildstad et al teaches away from achieving an engraftment rate of 100% for the organ from the graft donor.

Furthermore, one skilled in the art could not predict or expect a technique "achieving an engraftment rate of 100%" by the combination of Ildstad et al and Slavin et al.

In the present invention, the organ for transplanting must be derived from the same graft donor as the WBMC (see pages 27-28, Item (5) of Test Example 4 of the present specification). Thus, Claim 9 has been amended to more clearly set forth such.

Finally, the Examiner contends that with respect to the references cited by the Applicants, the experiments described by Ikebukuro et al and Hayashi et al can not be used because said references use a different experimental procedure, i.e., a recipient-lethal irradiation of 10 Gy and T cell depleted bone marrow transplantation.

Ikebukuro et al uses rats as test animals. Unlike mice, rats have a relatively high resistance to irradiation (a mouse has relatively higher radiation sensitivity than a rat). 9 Gy disclosed in Ikebukuro et al is not lethal, but sublethal (as disclosed in line 3 of the abstract of Ikebukuro et al: "sublethal irradiation (9Gy)"). Therefore, Applicants respectfully disagree with the Examiner's position.

Based on the teachings of Ikebukuro et al, it is clear that the method disclosed in Ildstad et al causes rejection of transplanted organs and cannot achieve 100% engraftment.

The Examiner is requested to note that the determination of sublethal or lethal depending on the difference in the animal species employed is not subject to the sensitivity of BMCs to irradiation, but to the sensitivity of each organ (pancreas,

kidney, liver, etc.) of the animals to irradiation. The sensitivity of BMCS themselves is believed to be substantially the same.

As described above, Ildstad et al teaches a technique that has a critical drawback where the number of donor orientated BMCs decreases with time and the transplanted organ is accordingly rejected. Ildstad et al does not disclose a technique by which 100% engraftment is achieved according to a one-day protocol.

Therefore, it is clear that one of ordinary skill in the art could not arrive at the present invention from any combination of the teachings of Ildstad et al with those of Slavin et al, because Slavin et al also does not teach a technique by which 100% engraftment is achieved according to a one-day protocol by employing TBI.

The Examiner contends that Zhang et al teaches that in both i.v. and p.v. injections of BMC, most of the cells migrate to the liver, although more BMCs do so after p.v. administration than after i.v. administration, and that Zhang et al reviews the art recognized prolongation of organ graft survival in a recipient when cells from the donor are administered to the recipient via p.v. in addition to the transplanted organ.

However, Zhang et al merely discloses the results of a comparison between i.v. and p.v. in a system <u>without</u> irradiation. Applicants respectfully submit that it is <u>impossible</u> to predict whether similar effects occur in a system <u>with</u> irradiation, as claimed in the present invention.

The technique taught by Slavin et al, wherein immunological tolerance is given by employing TBI and the technique disclosed in Zhang et al, wherein irradiation is not preformed, are fundamentally different in whether or not the recipient's general immune system itself is damaged. Thus, one skilled in the art would not expect that the difference in results attributable to the difference in the administration route, i.e., i.v. and p.v., disclosed in Zhang et al would be applicable to a recipient who has undergone TBI, as claimed in the present invention. This is because the immune system and liver of the recipient are damaged by TBI, and therefore rejection of administered WBMCs differs.

Specifically, it is apparent to ones skilled in the art tht the results obtained by the non-TBI system (TBI dose of 0 Gy) disclosed in Zhang et al can not be applied to a TBI system. In other words, a skilled artisan would not foresee the effects achieved by TBI plus p.v. from the teachings of Ildstad et al in view of Zhang et al. This is clear from the Examiner's assertion that Hayashi et al and Takao et al (of record) can not be used to infer the results of Ildstad et al. That is, it is the Examiner's position that even in systems of irradiation, if the radiation doses are different, the results can not be inferred. Thus, in view of the Examiner's assertion, there is no way that a person skilled in the art could predict that similar effects can be attained when the techniques used in a non-irradiation system are employed in a system with irradiation.

Neither Slavin et al nor Zhang et al disclose a technique usable for a one-day protocol by which an engraftment rate of 100% can be achieved by employing the immunological tolerance technique using TBI. Thus, Applicants submit that one skilled in the art could not predict that a technique achieving 100% engraftment according to a one-day protocol from a combination of Slavin et al, Ildstad et al and Zhang et al.

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested by Slavin et al alone or when combined with the teachings of Ildstad et al and Zhang et al, and in any event, such a combination can only be made in hindsight, which is legally improper. Thus, Applicants request withdrawal of the Examiner's rejection.

In view of the amendment to Claim 9 and the arguments set forth above, reexamination, reconsideration and allowance are respectfully requested.

The Examiner is invited to contact the undersigned at the telephone number listed below on any questions that might arise.

Respectfully submitted,

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WASHINGTON OFFICE
23373
CUSTOMER NUMBER

Date: November 22, 2004